UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,303	11/04/2005	Peter Bernstein	133087.12001(100819-1PUS)	5966

52286 7590 12/21/2007

Pepper Hamilton LLP
400 Berwyn Park
899 Cassatt Road
Berwyn, PA 19312-1183

EXAMINER	
O'DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
12/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,303	BERNSTEIN ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,7,10 and 16-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7,10 and 16-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9 November 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-4, 6, 7, 10, 16-28 are pending in the current application.

2. The instant application is a 371 of PCT/SE2003/001329, filed August 26, 2003, which claims the priority of Application No. 0202567-4 filed in Sweden on August 29, 2002 and Application No. 0202986-6 filed in Sweden on October 9, 2002.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 9, 2007 has been entered.

Response to Arguments

3. Applicant's arguments filed on November 9, 2007 have been fully considered but they are not fully persuasive. With respect to the rejection under 35 U.S.C. 112 1st paragraph for **scope** of enablement in regards to the compound claims, the examiner appreciates the claim amendments with regard to the substituents on R4, however the naphthyl moiety R1 substituents contain numerous inoperative embodiments in particular the olefins and alkynes and the Ra and Rb taken together to form a ring. If these embodiments were removed the scope of the claim would be acceptable. The rejections under 35 U.S.C. 112 1st paragraph for **lack** of enablement for treating various diseases and disorders with the compounds of the instant case is also maintained for the reasons of record. The examiner greatly appreciates the removal of many of the previous diseases ("kleptomania" etc.) and wishes to thank the applicant for doing so. This will no doubt

provide a more focused examination. The remaining claims are drawn to treating depression in its various forms and anxiety. The applicant may be correct in the interpretation of the Rosenzwieg-Lipson reference, however after reviewing the state of the art anew, the previous position is further substantiated with the following citation:

"Antidepressant efficacy of the NK1 antagonist Aprepitant (MK869) (6) could be demonstrated in a placebo controlled clinical study where a dose of 300 mg (p.o., once daily) of Aprepitant was administered to patients suffering from major depressive disorder for 6 weeks. In this study, Aprepitant was well tolerated and the effectiveness of the compound as an antidepressant agent was comparable with that of the serotonin uptake inhibitor paroxetine [22, 23]. **In later studies, however, the antidepressant activity of Aprepitant could not be confirmed** [24]. In summary, **the existing experimental evidence suggest that substance P and the NK1 receptor are important players in the pathophysiology of central nervous diseases such as depression [18], however, the partially negative results with Aprepitant are contradictory to this and additional studies will be needed to get conclusive answers on the antidepressant potential of neurokinin antagonists.**" MARC GERSPACHER "Selective and Combined Neurokinin Receptor Antagonists" *Progress in Medicinal Chemistry* **2005**, *43*, 49-103

This reference serves to illustrate the very real lack of unpredictability even with clinical data. Here we have only the cell based assays. A new ground of rejection based upon new art found by the examiner is recorded, and further impacts two double patenting rejections, as well as the previously indicated allowable subject matter.

Objections

Claim 24 is objected to for a minor spelling error, Pg. 10 claim 24 recites:

1-N-Methyl-4-(3-fluorophenyl)-4-(3-(3-cyano-2,4-dimethoxynaphth-1-yl)-3-ox-o-2-azaprop-1-yl)piperidine;

"oxo-o" seems to have been meant to be"oxo". The examiner is somewhat confused by the nomenclature used here (claim 24). In some cases the compounds are named as piperidines and other as napthamides. Is their a reason for this?

Claim Rejections - 35 USC § 112

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. By deleting the proviso below from claim 1 with the amendments:

~~... oxygen or sulfur, j is 0, 1, 2, 3 or 4, and k is 0, 1 or 2;~~

m is 1, 2 or 3 ~~where at least one R^1 moiety is other than hydrogen~~;

A genus of compounds not described in the specification has been created.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

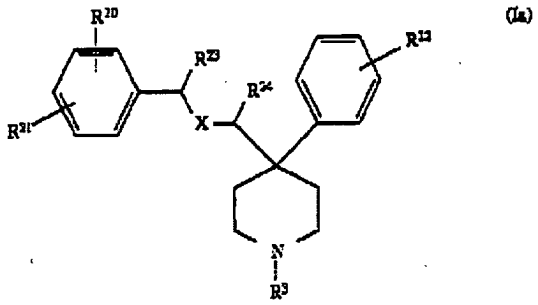
4. Claims 1-4, 6, 7, are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrison et. al. U. S. patent 5,620,989 in view of Bernstein et. al. WO 00/02859 (cited on the IDS). The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

(MPEP 2141.01)

Harrison et. al. teaches NK-1 antagonists that are analogs of the compounds of the instant case that have the same utility. In particular the genus shown below:

A particular sub-class of compounds according to the invention is represented by compounds of formula (Ia), and salts and prodrugs thereof:



(Ia)

Bernstein et. al. teach piperidinyl naphthyl amide compounds that are remarkably similar in structure and have the same utility.

Ascertainment of the difference between the prior art and the claims

The instant claims differ from the compounds of Harrison et. al only in the substitution of a naphthyl amide group for phenoxy. The compounds may also be seen as involving a substitution of a piperidinyl ethyl moiety for a quaternary piperiidine. These relationships are illustrated graphically in Figure 1:

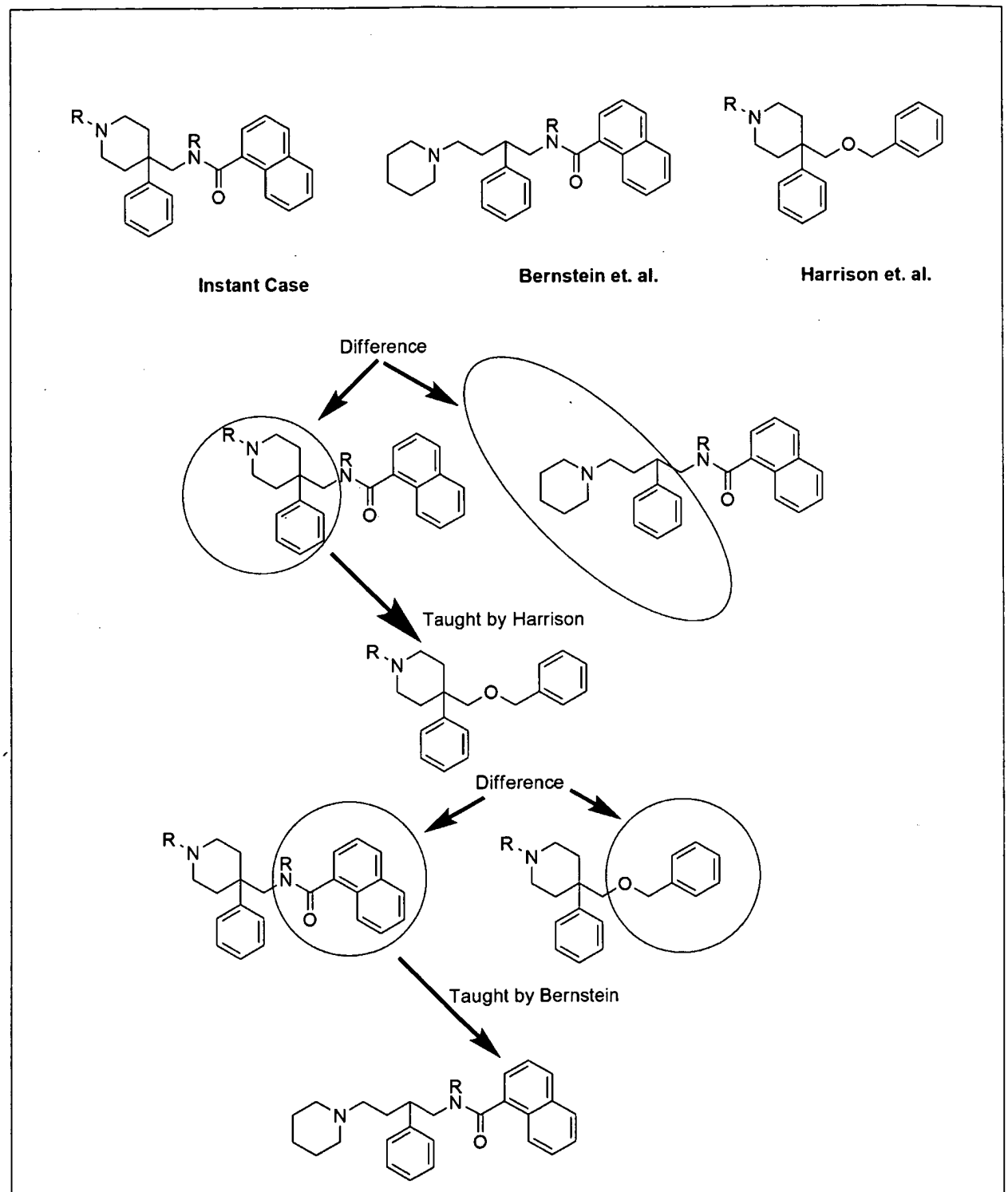


Figure 1. The difference between the prior art and the instant claims.

Finding of prima facie obviousness

Rational and Motivation

(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use analogs of those of Harrison et. al. to produce the instant invention. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these compounds on the expectation that such close analogues would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. It would be routine for the chemist to make this change since the quaternary piperidines had already been prepared and shown to be potent.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One of ordinary skill is also one of "ordinary creativity, not an automaton". See Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc. UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT "An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Claim Rejections 35 U.S.C 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1 & 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds of structural diagram I (claim 1), it does not reasonably provide enablement for the multivariate structures contained in the claim where R^1-R^2 are varied substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to prepare the compounds of the invention commensurate in scope with these claims. As per MPEP:

> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. **The same can be said if certain chemicals are required to make a compound or practice a chemical process.** In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981). (emphasis added)

Based on applicants disclosure (on pages 16 and 17 of the specification, reproduced below for clarity),

The requisite 1-N-BOC-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl)piperidine was prepared as follows:

a) 1-N-BOC-4-(3,4-dichlorophenyl)-4-(3-(3-cyano-2-methoxynaphth-1-yl)-3-oxo-2-azaprop-1-yl) piperidine.

To a stirred solution containing 1-N-BOC-4-aminomethyl-4-(3,4-dichlorophenyl)piperidine (260.8 mg, 0.726 mmol), 3-cyano-2-methoxy-1-naphthoic acid (164.6 mg, 0.724 mmol), HOBT hydrate (290 mg, 1.89 mmol), N-methylmorpholine (0.17 mL), and DCM (15 mL) was added 1-(3-(dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (215.5 mg, 1.12 mmol). After 72h, the mixture was diluted with 30% hexane/EtOAc, washed successively with water (2X), 0.1 N aq. HCl (2X), sat. aq. $NaHCO_3$, dried, filtered, and concentrated. The residue was purified by chromatography (0-1% MeOH/DCM) to give the title compound as a white, foamy solid. MS m/z 468.

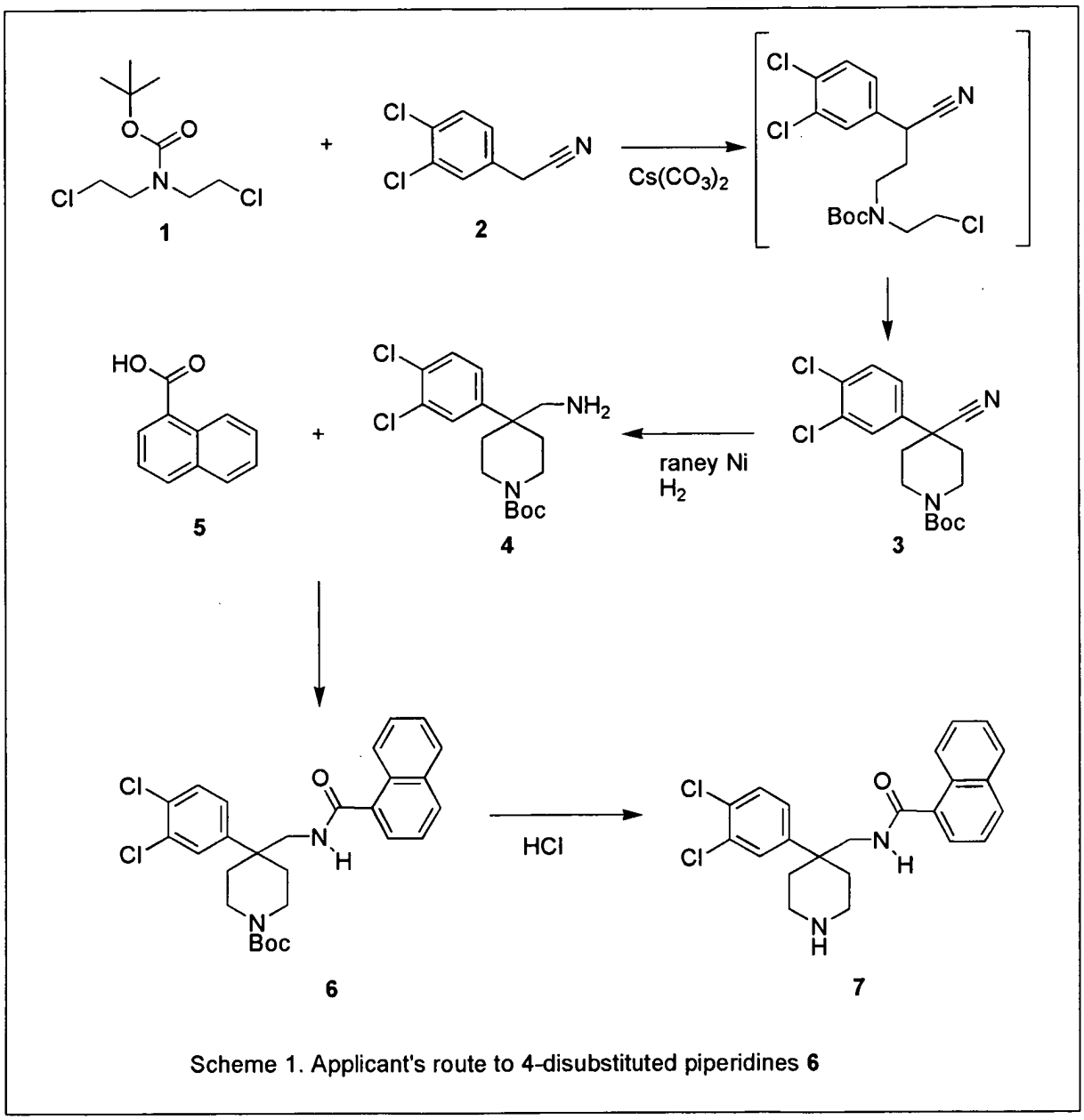
b) 1-N-BOC-4-aminomethyl-4-(3,4-dichlorophenyl)piperidine

A mixture containing 1-N-BOC-4-(3,4-dichlorophenyl)-4-cyanopiperidine (5.25 g, 14.78 mmol), Raney Ni catalyst (5g of 50% aq. slurry), EtOH (175 mL), and ammonium hydroxide (88 mL) was placed under a hydrogen atmosphere (50 psi) and agitated (Parr apparatus) for 18 h. The mixture was filtered through diatomaceous earth, concentrated, and purified by chromatography (0-5% MeOH/DCM) to give the title compound as an off-white solid. MS m/z 344 ($M+1-CH_3$). 1H NMR ($CDCl_3$) δ 7.44 (d, 1H), 7.38 (d, 1H), 7.15 (m, 1H), 3.7 (br d, 2H), 3.07 (m, 2H), 2.76 (s, 2H), 2.08 (br d, 2H), 1.71 (m, 2H), 1.44 (s, 9H).

c) 1-N-BOC-4-(3,4-dichlorophenyl)-4-cyanopiperidine

A solution containing bis(2-chloroethyl)-N-BOC amine (described in US Patent 5,661,163) (8.15 g, 33.67 mmol), 3,4-dichlorophenylacetonitrile (5.05 g, 27.17 mmol), and DMSO (50 mL) was stirred at RT and solid cesium carbonate (17.6 g, 54.02 mmol) was added (in portions) over 10 minutes. After 20 h, additional cesium carbonate (1.7 g,) was added, and the mixture stirred for an additional 72 h. The mixture was partitioned between water and EtOAc, the aq. layer was removed, and the organic layer washed successively with additional water, 0.1M aq. HCl (2X), sat. aq. $NaHCO_3$, and brine. The organic layer was dried, filtered, concentrated, and the residue triturated (3:1 hexane/ethyl acetate) to give the title compound as an off-white solid, m.p. 142-145 °C. MS m/z 255 . 1H NMR ($CDCl_3$) δ 7.55 (d, 1H), 7.49 (d, 1H), 7.32 (m, 1H), 4.3 (br d, 2H), 3.18 (br t, 2H), 2.07 (d, 2H), 1.89 (m, 2H), 1.48 (s, 9H).

Scheme 1 was constructed and is presented here for discussion of the synthetic route to these compounds and the limitations therein.



Scheme 1. Applicant's route to 4-disubstituted piperidines **6**

Compounds bearing a vast list of possibilities for R1, R^2, R^3, R^4 have been claimed in claims 1-3 and very little guidance has been provided on how to do so. A detailed discussion of each limitation of the synthesis as it relates to the claims at hand

(claims 1 & 6) will be provided. The main thrust of applicant's argument appears to be that a chemist can simply make any compound at will, which is inconsistent with the state of the art. As stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)....." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

The naphthoic acids such as **5** (Scheme 1) required for the scope of this invention are not commercial. Thus the substituent R_1 depends upon these compounds It is recognized that applicant makes reference to a prior commonly assigned application WO 00/20389 for the preparation of a good portion of these and these will be considered allowable, particularly where applicant has working examples in synthetic schemes, but the recitation of olefins, alkynes, and fused rings on Ra and Rb in particular seem very difficult to prepare and the specification does not bear these susbtituents out.

Another serious consideration is the "how to use" requirement of 112 1st which mandates that this genus must be constructed such that the members have the property of NK1/SRI activity. What are the effects of theses olefins alkynes and fused rings? We do not know but in this case the members of the genus bear no structural resemblance to one another and even if they did the situation is far from clear that they would have the desired activity. As one reviewer stated, Martin, Yvonne C. et. al. "Do Structurally Similar Molecules Have Similar Biological Activity?" *Journal of Medicinal Chemistry* **2002**, *45*, 4350-4358:

> "..... compounds that look very similar to a chemist sometimes bind in very different orientations in the protein active site, bind to a different conformation of a protein, or bind to a different protein altogether.[15] In fact, such observations are why medicinal chemists need to make so many compounds to optimize the biological activity of a structural class, even when they are designing to a biological target of known structure...(pg. 4536 column 2, line 9).....This work also shows that the biological similarity is not so strong as has previously been assumed. For example, at ≥ 0.85 Tanimoto similarity in Daylight fingerprints, **only 30% of compounds similar to an active are themselves active**."(conclusions)

It is noted that all the working examples have a nitrile on the naphthyl ring. This would appear4 to be a critical factor governing activity at the NK1 Receptor. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a):

"A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification , at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)."

It is very clear that one could not make/use this very broad invention that has only a few working examples in this unpredictable art without undue experimentation.

From 11/326,084

6. Claims 10, 16-28 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Disclosure of the activity of the compounds and dosages that are critical or essential to the practice of the invention, but not included in the claims is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The only information given as to what these compounds may do, at least in the pharmacological sense, is on pg. 12 of the disclosure "Individual IC_{50} values were reported, along with plC_{50}. When the two IC_{50}'s obtained for a compound differed by more than 3-fold that compound was assayed one or two more times to redetermine the value. Compounds of the present invention exhibit a Ki in the range of 1 to 100 nM in the SERT assay and have an IC_{50}'s in the range 1 to l00 nM in FLIPR assay." The applicant has given ranges of two orders of magnitude for each individual assay, without reference to a known compound that is an agonist/inhibitor and the variability in these assays make evaluation of therapeutic value difficult. In the instant case we do not know whether the compounds are partial agonists at the NK-1 receptor. It is possibly that some compounds are both SERT inhibitors and partially active at the NK-1 receptor and vice versa, or both potent inhibitors of SERT and potent antagonists at the NK-1 receptor. Applicant seems to believe these compounds are the later although no support has been provided for this assertion. Moreover, even if this dual activity was possessed by the compounds of the invention, one cannot predict *a priori* what the outcome of such complex pharmacological behavior would be in the complex diseases of claim 10. The article cited by the authors (Ryckmans, T., et al., Bioorg. Med. Chem.Lett. (2002), 12, 261). suggests that these kinds of compounds might be useful for treatement of depression and they may well be but no such evidence is provided in the instant case. The "how to use" requirement of 35 U.S.C. 112 are not met by disclosing a pharmacological activity of the claimed compounds if one skilled in the art would not be able to

use the compounds effectively without undue experimentation (In re Diedrich (CCPA 1963) 318 F2d 946, 138 USPQ 128; In re Gardner et. al. (CCPA 1970) 427 F2d 786, 166 USPQ 138). The treatment of depression is not indicated by the state of the art, even with pre-clinical data (animal models), as stated in a recent review (Rosenzwieg-Lipson et. al. *Pharmacology & Therapeutics* **2007**, *113*, 134-153) pg. 140 paragraph 3 sentence 2:

> **"Although the NK-1 antagonist aprepitant was not proven efficacious in Phase III depression trials (Keller et al., 2006), it is conceivable that the combination of aprepitant with an SSRI might result in rapid onset of antidepressant effects. To this end, NK-1 antagonists have been shown to potentiate the neurochemical effects of SSRIs in preclinical studies** (Guiard et al., 2004). **Whether this combination or other non-monoaminergic mechanisms will produce rapid onset antidepressant effects remains to be answered."**

Thus the state of the art in the area of these dual antagonists is murky at best. Even if there was a correlation of the pharmacological activity with a clinical manifestation, we have only *in-vitro* testing of these compounds and no *in-vivo* data. Without at least animal studies of *in-vivo* activity one cannot believe that these compounds will behave as therapeutics in those suffering from depression. Moreover, even if these compounds were evaluated simply as NK-1 antagonists, a recent review article (McLean, S. *Current Pharmaceutical Design* **2005**, *11*, 1529, pg. 1542 paragraph 3) states, that:

> In summary, clinical studies with three different compounds demonstrate antidepressant efficacy in both mildly depressed as well as melancholic patients. Furthermore, the favorable side effect profile of the agents suggests a viable therapy particularly for people experiencing significant sexual side effects with currently available antidepressants. **This has to be balanced against a number of trials in which NK1 receptor antagonists failed to show activity. In addition to the previously mentioned negative trials, NKP608 another NK1 receptor antagonist was reported on the Novartis web site to have been terminated from further development for depression although it is unclear whether this**

> **was due to side effects or lack of efficacy. To date there are three positive trials in depression, one positive trial in panic, several failed trials and at least 2 negative studies.**

It seems very unlikely that one skilled in the art would know what to do with these compounds. and the data given here do not correlate with the treatment given the mechanism that applicant alleges and the current knowledge in the art.

As per MPEP:

CORRELATION: IN VITRO /IN VIVO
The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. **If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition.** In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications). Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example. A rigorous or an invariable exact correlation is not required, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985): [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

After reviewing the state of the art anew, the previous position is further substantiated with the following citation:

"Antidepressant efficacy of the NK1 antagonist Aprepitant (MK869) (6) could be demonstrated in a placebo controlled clinical study where a dose of 300 mg (p.o., once daily) of Aprepitant was administered to patients suffering from major depressive disorder for 6 weeks. In this study, Aprepitant was well tolerated and the effectiveness of the compound as an antidepressant agent was comparable with that of the serotonin uptake inhibitor paroxetine [22, 23]. **In later studies, however, the antidepressant activity of Aprepitant could not be confirmed** [24]. In

summary, **the existing experimental evidence suggest that substance P and the NK1 receptor are important players in the pathophysiology of central nervous diseases such as depression [18], however, the partially negative results with Aprepitant are contradictory to this and additional studies will be needed to get conclusive answers on the antidepressant potential of neurokinin antagonists.**" MARC GERSPACHER "Selective and Combined Neurokinin Receptor Antagonists" *Progress in Medicinal Chemistry* **2005**, *43*, 49-103

This receptor is a GPCR with a vast number of binding sites and conformations each of which may be associated with a distinct physiological outcome. One reviewer has summarized the situation this way (Terry Kenakin and Ongun Onaran "The ligand paradox between affinity and efficacy: can you be there and not make a difference?" *TRENDS in Pharmacological Sciences* **2002**, *23*, 275-280):

"A probabilistic model of protein conformation can be used to quantify the probability of various receptor conformations and the effect of ligand binding on those conformations. The basic idea behind the probabilistic model is that the function of a receptor protein is not assigned to particular conformations of the receptor. Instead, the function arises as a result of ligand-induced perturbation of the distribution of conformational states over the conformational space of the receptor.....**The foregoing discussion leads to the general conclusion that if a ligand binds to the receptor, it most probably will produce a bias in the conformations of the receptor ensemble** [i.e. it will change the receptor by its presence (Fig. 3)]. Therefore, this suggests that all ligands with macro-affinity should be extensively studied for pharmacological activities other than simple G-protein activation because various physiological activities have been defined that are mediated by conformations not necessarily related only to G-protein activation..... Ligand activities that are not related to a standard G-protein-mediated physiological response **might have therapeutic utility**.

Here we have exactly this situation, namely a ligand with affinity, but no known function, which as Kenakin et. al. concluded "...the discovery of macro-affinity of a ligand for a receptor should be considered only a starting point for the optimal exploitation of a drug for therapeutic utility." The factors outlined in *In re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to use"...."the claimed invention without undue experimentation. *In re Wright* 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)."

It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

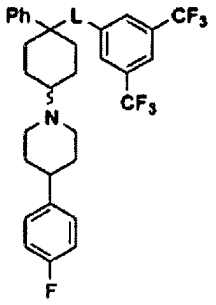
7. Claims 1-4, 6, 7, 10, 16-28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 10/539,140 in view of Elliot et. al. Bioorganic & Medicinal Chemistry Letters 12 (2002) 1755–1758.

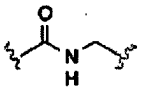
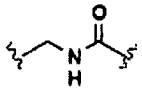
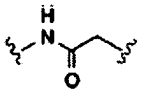
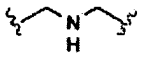
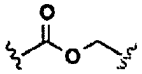
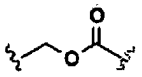
This is a provisional obviousness-type double patenting rejection. The instant claims differ from those of the '140 application by the identity of the moiety linking the naphthyl ring to the piperidine. This change is taught by Elliot et. al. in his NK-1 antagonists.

"Table 1 summarises the effect of modifications to the amide linker of 2. Throughout, trans-isomers have higher affinity than the corresponding cis-isomers. **A number of different linkers are tolerated, most notably**

the amides 2 and 15, the amine 17 and ether 23. The relatively poor affinity of the propyl linker 24 (hNK_1 IC_{50} 40nM) shows that a heteroatom in the chain is beneficial. This could be because the heteroatom introduces a conformational bias which favours binding, or due to participation of the heteroatom in a hydrogen bond to the receptor." Pg. 1756-1757 Bioorganic & Medicinal Chemistry Letters 12 (2002) 1755–1758

Table 1. Linker replacements



Compd	-L-	Stereochemistry	hNK_1 IC_{50} (nM)[a]
11		*cis*-	150±80
2		*trans*-	0.34±0.10
12		*cis*-	250±26
13		*trans*-	6.3±2.5
14		*cis*-	85±46
15		*trans*-	0.70±0.44
16		*cis*-	82±0
17		*trans*-	1.7±0.6
18		*cis*-	140±49
19		*trans*-	2.5±0.6
20		*cis*-	50% @ 1000
21		*trans*-	120±99
22		*cis*-	59±18
23		*trans*-	4.2±1.9
24		1:1 *cis*- and *trans*-	40±3

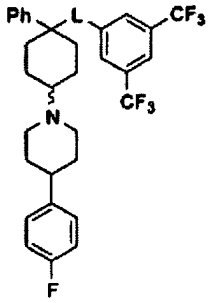
[a]Displacement of [^{125}I]-labelled substance P from the cloned receptor expressed in CHO cells. Data are mean ± SD (n = 3).[5]

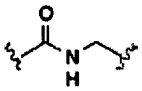
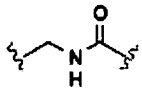
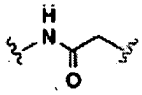
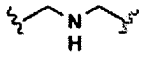
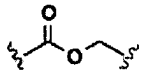
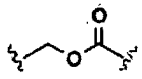
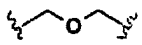
11. Claims 1-4, 6, 7, 10, 16-28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 10/527,280. The claims are coextensive in scope. in view of Elliot et. al. Bioorganic & Medicinal Chemistry Letters 12 (2002) 1755–1758.

This is a provisional obviousness-type double patenting rejection. The instant claims differ from those of the '280 application by the identity of the moiety linking the naphthyl ring to the piperidine. This change is taught by Elliot et. al. in his NK-1 antagonists.

"Table 1 summarises the effect of modifications to the amide linker of 2. Throughout, trans-isomers have higher affinity than the corresponding cis-isomers. **A number of different linkers are tolerated, most notably the amides 2 and 15, the amine 17 and ether 23.** The relatively poor affinity of the propyl linker 24 (hNK_1 IC_{50} 40nM) shows that a heteroatom in the chain is beneficial. This could be because the heteroatom introduces a conformational bias which favours binding, or due to participation of the heteroatom in a hydrogen bond to the receptor." Pg. 1756-1757 Bioorganic & Medicinal Chemistry Letters 12 (2002) 1755–1758

Table 1. Linker replacements



Compd	-L-	Stereochemistry	hNK$_1$ IC$_{50}$ (nM)[a]
11		*cis*-	150±80
2		*trans*-	0.34±0.10
12		*cis*-	250±26
13		*trans*-	6.3±2.5
14		*cis*-	85±46
15		*trans*-	0.70±0.44
16		*cis*-	82±0
17		*trans*-	1.7±0.6
18		*cis*-	140±49
19		*trans*-	2.5±0.6
20		*cis*-	50% @ 1000
21		*trans*-	120±99
22		*cis*-	59±18
23		*trans*-	4.2±1.9
24		1:1 *cis*- and *trans*-	40±3

[a]Displacement of [^{125}I]-labelled substance P from the cloned receptor expressed in CHO cells. Data are mean±SD (n = 3).[5]

This is a provisional obviousness-type double patenting rejection.

Conclusion

9. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

10. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

R Desai 12/18/07

D.K.O.

RITA DESAI
PRIMARY EXAMINER